SYNTHESIS AND SPECTRAL PROPERTIES OF SUBSTITUTED 1,4-DIHYDROPYRIDINES AND 1,4,5,6,7,8-HEXAHYDROQUINOLINES

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Cyclocondensation of 5-nitrophenyl-2-furaldehydes or 5-nitrophenyl-2-thiophenecarbaldehydes with acetoacetates and ammonia in organic solvents afforded 1,4-dihydropyridine derivatives, with 3-aminocrotonates and dimedone the former yielded 1,4,5,6,7,8-hexahydroquinoline derivatives. Relation between the structure and spectral properties is discussed.

Esters of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid and 1,4,5,6,7,8-hexahydro-5-oxoquinoline-3-carboxylic acid having either a suitably substituted aryl ($-NO_2$, $-CF_3$, $-Cl$ *etc.*) or a five or six-membered heterocycle (furyl, thienyl, pyridyl) are known to exhibit a coronary-dilatational activity[1-3]. So far, only few papers dealing with the synthesis of 4-(5-substituted-2-furyl)-1,4-dihydropyridine derivatives have been published[4,5] in the 1,4-dihydropyridine series of compounds.

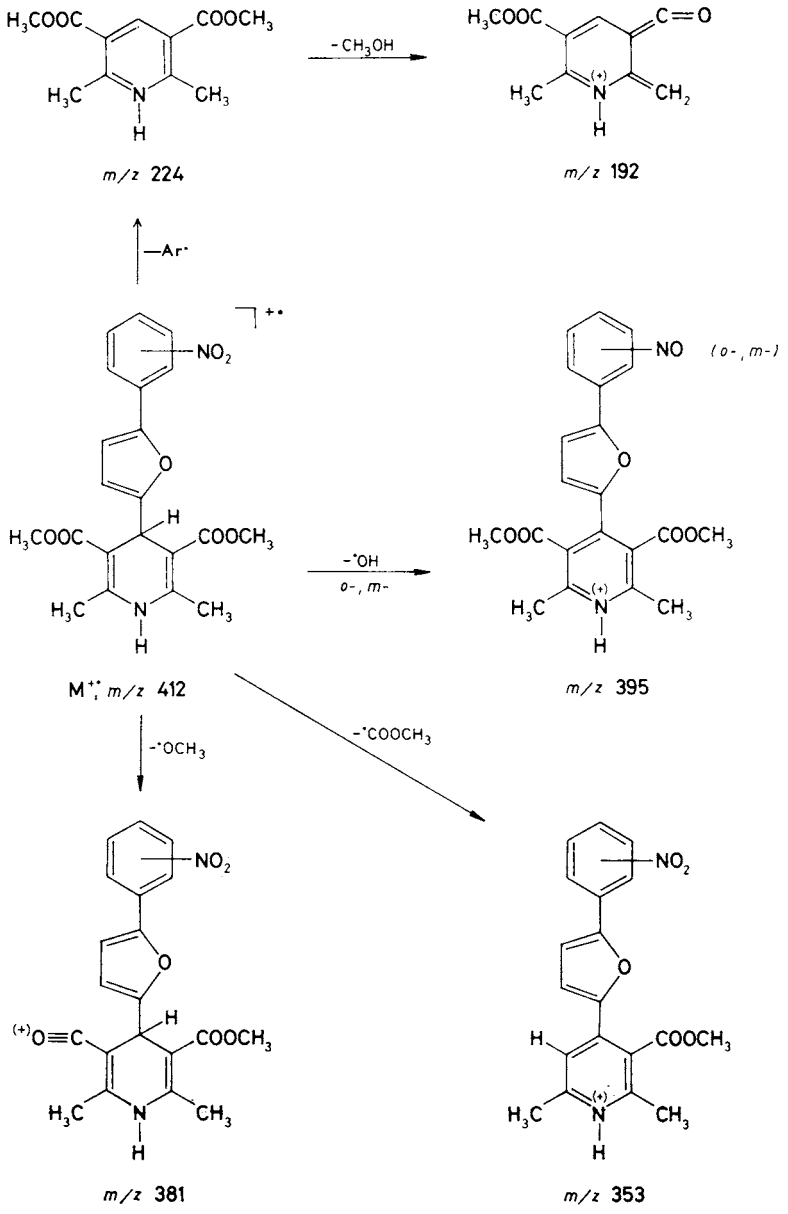
To investigate the coronary-dilatational effect and the physicochemical properties of these substances diesters of 2,6-dimethyl-4-(5-nitrophenyl-2-furyl)-1,4-dihydropyridine-3,5-dicarboxylic acid *I*, 2,6-dimethyl-4-(5-nitrophenyl-2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylic acid *II* and esters of 2,7,7-trimethyl-4-(5-nitrophenyl-2-furyl)-1,4,5,6,7,8-hexahydro-5-oxoquinoline-3-carboxylic acid *III* were synthesized.

EXPERIMENTAL

The reaction course and the purity of compounds were checked by thin-layer chromatography on DC-sheets Alufolien Kieselgel 60 F_{254} (Merck); the spots were detected either with iodine vapours or by UV light. Melting points were measured on a Boetius micro hot-stage. The IR spectra were recorded with a Perkin–Elmer, model 457 spectrophotometer in the 500—3 800 cm^{-1} range (2 mg of the substance in 200 mg of KBr), the electronic absorption spectra (concentration $3-5 \cdot 10^{-5}$ mol l^{-1} in methanol at 25°C) were run with a Specord UV-VIS apparatus (Zeiss, Jena) in 1 cm-cells. The ^1H NMR spectra of hexadeuteriodimethyl sulfoxide solutions were measured at 25°C with a Jeol FX 100 instrument operating at 95·54 MHz, tetramethylsilane being the internal reference; the mass spectra were recorded with a Jeol JMS D 100 spectrometer at 70 eV electron energy.

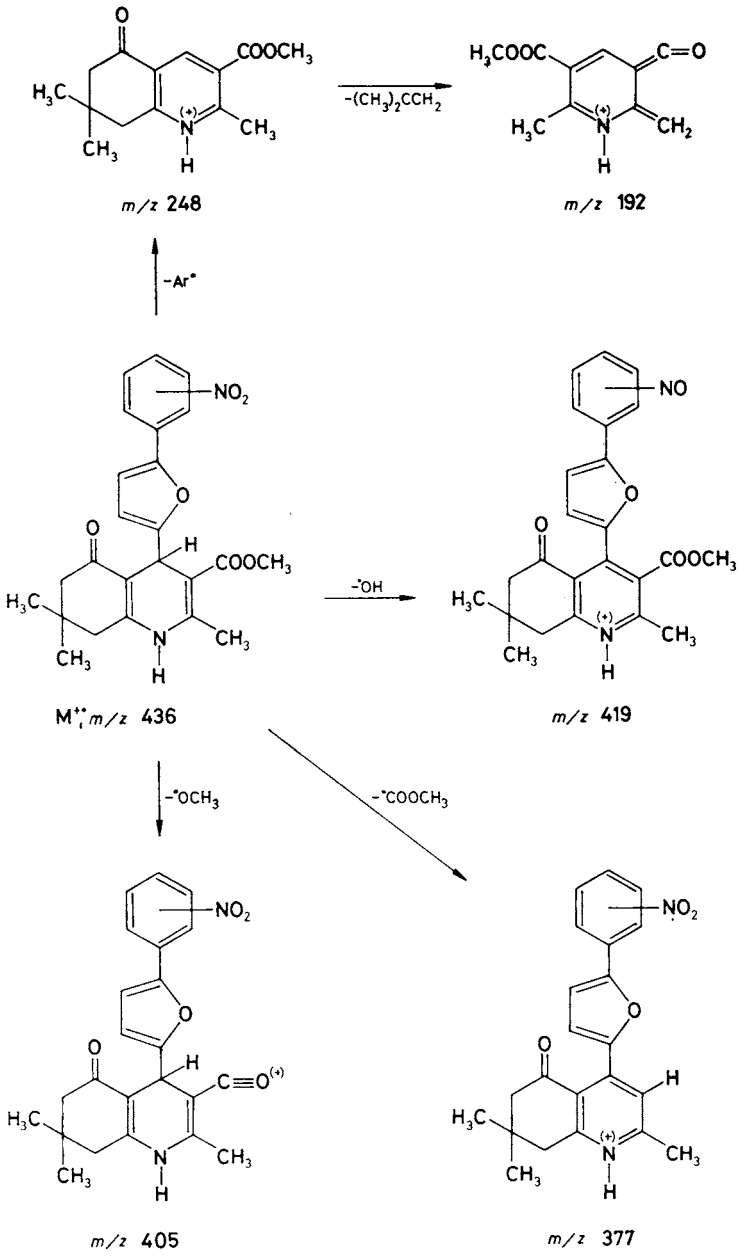
The starting 5-nitrophenyl-2-furaldehydes and 5-nitrophenyl-2-thiophenecarbaldehydes were prepared by the Meerwein–Müller arylation of furaldehyde or 2-thiophenecarbaldehyde with diazonium 2-, 3- or 4-nitranilines[6,7]. Esters of acetoacetic acid were obtained by addition of the

respective alcohol to the diketene[8], esters of 3-aminocrotonic acid by reacting the former with ammonia[9]. Dimedone was the commercial product of Fluka (Switzerland).



In the upper left formula (m/z 224) for N read $\overset{(+)}{N}$.

SCHEME 1



In formula $M^{+\cdot}$, m/z 436 the denotation $\neg^{+\cdot}$ is missing in the upper right side.

SCHEME 2

TABLE I

Esters of (5-nitrophenyl-2-furyl)-1,4-dihydropyridine-3,5-dicarboxylic acid (*Ia*—*Ip*)

Compound		Formula M_r	Calculated/found			M.p., °C (Yield, %)
R	Y		% C	% H	% N	
	Ia	$C_{21}H_{20}N_2O_7$	61·16	4·89	6·79	190—191
CH_3	2-NO_2	412·4	61·16	4·86	6·76	(70)
	Ib	$C_{21}H_{20}N_2O_7$	61·16	4·89	6·79	218—219
CH_3	3-NO_2	412·4	60·95	4·92	7·00	(61)
	Ic	$C_{21}H_{20}N_2O_7$	61·16	4·89	6·79	200—201
CH_3	4-NO_2	412·4	61·23	4·92	7·00	(66)
	Id	$C_{23}H_{24}N_2O_7$	62·67	5·49	6·36	125—126
C_2H_5	2-NO_2	440·4	62·68	5·51	6·29	(70)
	Ie	$C_{23}H_{24}N_2O_7$	62·67	5·49	6·36	156—158
C_2H_5	3-NO_2	440·4	62·67	5·47	6·38	(65)
	If	$C_{23}H_{24}N_2O_7$	62·67	5·49	6·36	179—180
C_2H_5	4-NO_2	440·4	62·53	5·44	6·29	(70)
	Ig	$C_{25}H_{28}N_2O_7$	64·09	6·02	5·98	128—130
$CH(CH_3)_2$	2-NO_2	468·5	64·01	6·00	5·82	(64)
	Ih	$C_{25}H_{28}N_2O_7$	64·09	6·02	5·98	145—147
$CH(CH_3)_2$	3-NO_2	468·5	64·12	6·10	6·01	(70)
	Ii	$C_{27}H_{32}N_2O_7$	65·30	6·45	5·64	140—141
$C(CH_3)_3$	2-NO_2	496·5	65·37	6·43	5·63	(60)
	Ij	$C_{27}H_{32}N_2O_7$	65·30	6·45	5·64	178—179
$C(CH_3)_3$	3-NO_2	496·5	65·28	6·47	5·69	(65)
	Ik	$C_{31}H_{32}N_2O_7$	68·36	5·92	5·14	175—177
C_6H_{11}	2-NO_2	544·6	68·28	5·76	5·06	(72)
	Il	$C_{31}H_{32}N_2O_7$	68·35	5·92	5·14	192—193
C_6H_{11}	3-NO_2	544·6	68·13	5·68	5·02	(80)
	Im	$C_{25}H_{20}N_2O_7$	65·21	4·37	6·08	140—142
$CH_2C{\equiv}CH$	2-NO_2	460·4	65·17	4·38	6·09	(65)
	In	$C_{25}H_{20}N_2O_7$	65·21	4·37	6·08	156—158
$CH_2C{\equiv}CH$	3-NO_2	460·4	65·29	4·33	5·88	(76)
	Io	$C_{29}H_{36}N_2O_9$	62·57	6·51	5·03	112—113
$CH_2CH_2OC_3H_7$	2-NO_2	556·6	62·49	6·62	4·93	(59)
	Ip	$C_{29}H_{36}N_2O_9$	62·57	6·51	5·03	120—122
$CH_2CH_2OC_3H_7$	3-NO_2	556·6	62·59	6·53	5·07	(65)

Esters of 2,6-*dimethyl*-4-(5-*nitrophenyl*-2-*furyl*)-1,4-*dihydropyridine*-3,5-*dicarboxylic acid* Ia—Ip. The 5-(2-, 3- or 4-nitrophenyl)-2-furaldehyde (0·1 mol), ester of acetoacetic acid (0·24 mol), aqueous ammonia (0·12 mol) and methanol or ethanol (20 ml) were refluxed for 5 to 7 h. The mixture was cooled, the crude product was filtered off and crystallized from ethanaol to which charcoal was added.

Esters of 2,6-*dimethyl*-4-(5-*nitrophenyl*-2-*thienyl*)-1,4-*dihydropyridine*-3,5-*dicarboxylic acid* IIa — IIf. A solution of 5-(2-, 3- or 4-nitrophenyl)-2-thiophenecarbaldehyde (0·1 mol), ester of acetoacetic acid (0·24 mol), concentrated ammonia (0·12 mol), and methanol or ethanol (25 ml) were refluxed for 6 to 8 h. The crude product separating after cooling was crystallized from methanol.

Esters of 2,7,7-*trimethyl*-4-(5-*nitrophenyl*-2-*furyl*)-1,4,5,6,7,8-*hexahydro*-5-*oxoquinoline*-3-*carboxylic acid* IIIa—IIIi. A mixture of 5-(2-, 3- or 4-nitrophenyl)-2-furaldehyde (0·1 mol), dimedone (0·1 mol), and methanol–acetic acid (8 : 3, 30 ml) was refluxed for 2 h. The separated crystals were filtered off and recrystallized from methanol.

RESULTS AND DISCUSSION

Esters of 2,6-dimethyl-4-(5-nitrophenyl-2-furyl)-1,4-dihydropyridine-3,5-dicarboxylic acid *I* (Table I) were prepared by a conventional Hantzsch cyclocondensation of 5-(2-, 3- or 4-nitrophenyl)-2-furaldehyde with esters of acetoacetic acid and ammonia in 40 to 80% yields. The 5-(2-, 3- or 4-nitrophenyl)-2-thiophenecarbaldehydes

TABLE II

Diesters of 2,6-dimethyl-4-(5-nitrophenyl-2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylic acid *IIa—IIf*

Compound		Formula	Calculated/found				M.p., °C
R	Y	M_r	% C	% H	% N	% S	(Yield, %)
	IIa	$C_{21}H_{20}N_2O_6S$	58·86	4·70	6·54	7·48	185—186
CH_3	2-NO_2	428·5	58·62	4·64	6·44	7·36	(50)
	IIb	$C_{21}H_{20}N_2O_6S$	58·86	4·70	6·54	7·48	224—225
CH_3	3-NO_2	428·5	58·60	4·51	6·57	7·70	(56)
	IIc	$C_{21}H_{20}N_2O_6S$	58·86	4·70	6·54	7·48	238—240
CH_3	4-NO_2	428·5	58·66	4·59	6·48	7·62	(58)
	IId	$C_{23}H_{24}N_2O_6S$	60·51	5·30	6·13	7·02	160—161
C_2H_5	2-NO_2	456·5	60·64	5·23	6·21	6·95	(40)
	Ie	$C_{23}H_{24}N_2O_6S$	60·51	5·30	6·13	7·02	173—174
C_2H_5	3-NO_2	456·5	60·56	5·21	6·01	6·91	(48)
	IIf	$C_{23}H_{24}N_2O_6S$	60·51	5·30	6·13	7·02	182—184
C_2H_5	4-NO_2	456·5	60·58	5·27	6·12	7·05	(50)

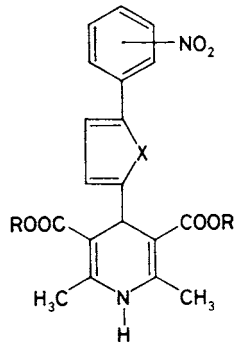
gave in an analogous way esters of 2,6-dimethyl-4-(5-nitrophenyl-2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylic acid *II* (Table II) in 40 to 58% yields. Esters of 2,7,7-trimethyl-4-(5-nitrophenyl-2-furyl)-1,4,5,6,7,8-hexahydro-8-oxoquinoline-3-carboxylic acid *III* (Table III) were obtained by the modified preceding procedure from 5-(2-, 3- or 4-nitrophenyl)-2-furaldehyde, an ester of 3-aminocrotonic acid and dimedone in 64 to 80% yield. The yields of compounds *IIq*–*IIf* are by 20% in average lower than those of *I* and *III* even though longer reaction times were applied; this is obviously due to a lower reactivity of 5-nitrophenyl-2-thiophenecarbaldehydes.

The ultraviolet absorption spectra of substituted 1,4-dihydropyridines *I* and *II* are characteristic of two absorption bands; band I at 232–237 nm (log ε, $m^2\ mol^{-1}$ 3·28–3·55), band II at 305–346 nm (log ε 2·94–3·59), Table IV. The *o*-nitrophenyl substituted derivatives *Ia* and *IIa* revealed three bands, this being in accordance with the reported data[3,10–13]. The UV spectra of 1,4,5,6,7,8-hexahydroquinolines *III* showed two absorption bands at 240–243 and 296–366 nm.

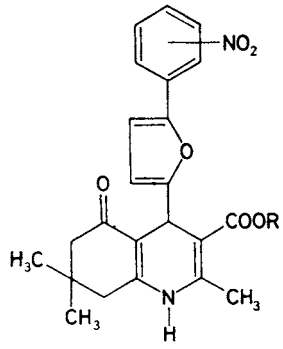
TABLE III

Esters of 2,7,7-trimethyl-4-(5-nitrophenyl-2-furyl)-1,4,5,6,7,8-hexahydro-5-oxoquinoline-3-carboxylic acid *IIIa*–*IIIi*

Compound		Formula M_r	Calculated/found			M.p., °C (Yield, %)
R	Y		% C	% H	% N	
	IIIa	$C_{24}H_{24}N_2O_6$	66·05	5·54	6·41	192–194
CH_3	2-NO_2	436·4	65·94	5·41	6·40	(67)
	IIIb	$C_{24}H_{24}N_2O_6$	66·05	5·54	6·41	242–243
CH_3	3-NO_2	436·4	66·07	5·54	6·35	(74)
	IIIc	$C_{24}H_{24}N_2O_6$	66·05	5·54	6·41	160–161
CH_3	4-NO_2	436·4	66·09	5·47	6·58	(74)
	IIId	$C_{25}H_{26}N_2O_6$	66·65	5·81	6·22	201–203
C_2H_5	2-NO_2	450·5	66·39	6·75	5·96	(71)
	IIIe	$C_{25}H_{26}N_2O_6$	66·65	5·81	6·22	200–202
C_2H_5	3-NO_2	410·5	66·67	5·64	6·28	(80)
	IIIf	$C_{26}H_{28}N_2O_6$	67·22	6·07	6·03	108–110
$CH(CH_3)_2$	2-NO_2	464·5	67·47	5·89	5·98	(77)
	IIIg	$C_{26}H_{28}N_2O_6$	67·22	6·07	6·03	183–185
$CH(CH_3)_2$	3-NO_2	464·5	66·91	5·89	6·08	(65)
	IIIh	$C_{26}H_{24}N_2O_6$	67·81	5·25	6·08	160–161
$CH_2C{\equiv}CH$	2-NO_2	460·4	67·62	5·43	6·08	(64)
	IIIi	$C_{26}H_{24}N_2O_6$	67·81	5·25	6·08	165–167
$CH_2C{\equiv}CH$	3-NO_2	460·4	67·67	5·12	6·10	(70)



I, X = O
II, X = S



III

TABLE IV

UV and IR spectra of compounds *Ia*—*Ic*, *IIa*—*IIc*, and *IIIa*—*IIIc*

Compound	UV spectrum		IR spectrum, cm^{-1}			
	λ_{max}, nm	log ε $m^2 mol^{-1}$	ν(N—H)	ν(=C—H)	ν)C=O)	ν(C=C)
Ia	236	3·51	3 330 s	3 086 w	1 691 s	1 662 s
	298	3·29				1 639 s
	345	3·17				
Ib	234	3·39	3 309 m	3 086 w	1 692 s	1 640 s
	305	3·52				
Ic	236	3·43	3 355 m	3 098 w	1 682 s	1 599 m
	318	3·28				1 650 s
IIa	235	3·37	3 349 s	3 092 w	1 693 s	1 644 s
	275	3·08				
	346	3·94				
IIb	237	3·55	3 329 m	3 089 w	1 695 s	1 650 s
	312	3·59				
IIc	232	3·28	3 340 m	3 095 w	1 699 s	1 594 m
	315	3·18				1 650 s
IIIa	240	3·42	3 286 m	3 080 w	1 695 m	1 602 s
	296	3·10				
IIIb	243	3·50	3 275 w	3 078 w	1 690 s	1 601 s
	303	3·40	3 200 m			
IIIc	240	3·42	3 280 m	3 080 w	1 694 m	1 607 s
	366	3·43				

The IR spectra of substituted 1,4-dihydropyridines are given in[3,10-13]. This group of compounds is characteristic mainly of stretching vibrations of the dihydropyridine skeleton, the furan and thiophene rings ν(C=C), ν(=C—H), ν(C=O) of

TABLE V

^{1}H NMR spectral data of compounds *Ia—Ic*, *IIa—IIc*, and *IIIa*

Compound	Chemical shifts δ, ppm				
	N—H	CH_3	$CH_{3_{ester}}$	H—4	$H_{fur(thien)}$ H_{arom}
Ia	9·06 s	2·28 s	3·61 s	5·02 s	6·03 (d, 1 H, H-3′) 6·78 (d, 1 H, H-4) 7·45—7·79 (m, 4 H, C_6H_4)
Ib	9·09 s	2·28 s	3·67 s	5·11 s	6·00 (d, 1 H, H-3′) 7·00 (d, 1 H, H-4) 7·72—8·58 (m, 4 H, C_6H_4)
Ic	9·11 s	2·29 s	3·66 s	5·13 s	6·07 (d, 1 H, H-3′) 7·11 (d, 1 H, H-4′) 7·70—8·30 (AA′BB′ 4 H, C_6H_4)
IIa	9·17·s	2·29 s	3·64 s	5·18 s	6·66 (d, 1 H, H-3′) 6·88 (d, 1 H, H-4′) 7·50—7·89 (m, 4 H, C_6H_4)
IIb	9·16 s	2·30 s	3·64 s	5·19 s	6·72 (d, 1 H, H-3′) 7·44 (d, 1 H, H-4′) 7·53—8·26 (m, 4 H, C_6H_4)
IIc	9·17 s	2·30·s	3·63 s	5·19 s	6·70 (d, 1 H, H-3′) 6·93 (d, 1 H, H-4′) 7·85—8·29 (AA′BB′, 4 H, C_6H_4)
IIIa	9·27 s	2·29 s	3·62 s	5·02 s	6·03 (d, 1 H, H-3′) 6·76 (d, 1 H, H-4′) 7·42—7·88 (m, 4 H, C_6H_4)

TABLE VI

Mass spectra of compounds *Ia—Ic*, *IIa*, and *IIIa—IIIc*

Compound	*m/z* (relative intensity, %)
Ia	412 (21), 397 (6), 395 (18), 381 (11), 353 (100), 224 (57), 192 (17)
Ib	412 (29), 397 (24), 395 (19), 381 (11), 353 (100), 224 (35), 192 (9)
Ic	412 (49), 397 (31), 381 (13), 353 (100), 224 (34), 192 (10)
IIa	428 (16), 413 (9), 411 (18), 397 (6), 369 (75), 224 (100), 192 (22)
IIIa	436 (35), 421 (6), 419 (79), 405 (9), 377 (34), 248 (100), 192 (19)
IIIb	436 (93), 421 (37), 419 (100), 405 (12), 377 (87), 248 (43), 192 (2)
IIIc	436 (100), 421 (38), 419 (22), 405 (66), 377 (74), 248 (90)

ester groups, and vibrations associated with the secondary amino group ν(N—H).

The ^{1}H NMR spectral data of *I*, *II*, and *III* are listed in Table V. The chemical shift values of protons H-4 and those of methyl groups attached in positions 2 and 6 of the dihydropyridine ring are in line with data reporting the chemical shift values for esters of 2,6-dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylic acid[14]; resonances of protons of phenyl, furyl and thienyl rings appeared in regions diagnostic of these groupings. Higher values for proton bound to dihydropyridine nitrogen indicate the formation of an intermolecular bridge with the solvent (hexadeuteriodimethyl sulfoxide).

Fragmentation patterns of derivatives *I* to *III* have many common features (*cf.* Table VI and Schemes 1 and 2). Loss of the aryl substituent from atom $C_{(4)}$ and formation of the ion at m/z $(M - Ar)^+$ (base peak) is diagnostic of 4-substituted 1,4-dihydropyridines[3,10,15]. An alternative fragmentation pathway for the above-mentioned compounds is the loss of OCH_3 radical under formation of the species at m/z $(M - OCH_3)^+$. Generally, two fragmentation patterns are characteristic; *a*) elimination of $^{\bullet}OH$ from ionized molecules; this step might be analogous with the photochemical decomposition of Nifedipin[11,16], *b*) elimination of $^{\bullet}OCOCH_3$ from the ionized molecules; this elimination predominantly occured with compounds having a furyl or thienyl group in the neighbourhood of the methoxycarbonyl grouping. It is quite probable that the heteroatom is a transmitter to mediate the hydrogen transfer to $C_{(3)}$; migration of the complete aryl residue could not be, however, excluded. Another prominent fragmentation is the retro Diels–Alder fission of ion $(M - Ar)^+$ giving rise to the species at m/z 192.

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